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A Systemic Approach For Developing A Robust Analytical Method: Analytical Quality By Design

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Abstract

The development of analytical procedures in a methodical manner is of the utmost significance in the pharmaceutical sector. It is of the utmost importance to strictly adhere to the norms and standards that have been created, such as those that have been developed by respectable organisations such as the International Council for Harmonisation (ICH) and the Food Development Administration (FDA). The concept of Quality by Design (QbD) is a fundamental idea that emphasises having a full understanding of both the product and the process, as well as including control and risk management. When compared to the conventional empirical method development, the science-based approach of Analytical Quality by Design (AQbD) offers a number of significant benefits. These advantages include the ability to get consistent results, the concentration on essential factors, and an increase in cost-effectiveness. In addition, the book digs into the primary factors that were reviewed throughout the process of method development. These criteria include specificity, linearity, limits of detection and quantitation, range, accuracy, and precision that was considered. In addition, it highlights the crucial role that regulatory organisations play in enhancing the quality of pharmaceuticals and in standardising the methods that are used for drug regulation on a global scale. Last but not least, it emphasises the value of AQbD in terms of facilitating regulatory communication, accelerating approval procedures, and monitoring alterations to analytical techniques once approval processes have been completed.

Keywords:

International Council for Harmonisation (ICH); Quality by Design (QbD); Analytical Quality by Design (AQbD); Food Development Administration (FDA).

1. Introduction

The evaluation of the characteristics of drug substances and products in relation to the acceptance criteria that have been established in advance for each characteristic is an essential part of the process of developing analytical methods.When beginning the process of designing a new analytical method, it is essential to pay serious thought to the selection of analytical instruments and technique. Emphasis should be made on ensuring that these choices are in line with the desired purpose and scope of the analytical method. During the process of method development, the International Council for Harmonisation (ICH) recommendations require that key characteristics such as specificity, linearity, limits of detection (LOD) and quantitation (LOQ), range, accuracy, and precision be evaluated [1].

The Food and Drug Administration (FDA) has been instrumental in the modernisation of regulatory procedures concerning pharmaceutical quality in the 21st century. This has been accomplished through the deployment of a risk-based strategy, which is formally known as the Pharmaceutical CGMP Initiative for the 21st Century. Within the context of these modernisation endeavours, the collaboration with international health and regulatory organisations has been an essential component. Through its participation in the International Council for Harmonisation (ICH), the Food and Drug Administration (FDA) has been able to significantly contribute to the development of a pharmaceutical quality system that is founded on an integrated approach to risk management and pharmaceutical research. The Food and Drug Administration (FDA) is actively participating in a variety of expert working groups within the International Council for Harmonisation (ICH) with the objective of developing recommendations that would expedite and standardise the procedures of drug regulation throughout all three regulatory areas. ICH Q4B, Q8, Q9, and Q10 are some of the criteria that stand out among them [2].

Quality by Design (QbD) in the pharmaceutical industry has experienced considerable advancements as a result of the establishment and implementation of recommendations developed by the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH), more especially. Q8 (R2), which stands for Pharmaceutical Development, Q9, which stands for Quality Risk Management, and Q10, which stands for Pharmaceutical Quality System) Within the pharmaceutical business, these recommendations have been significant in developing and improving the approach to pharmaceutical development, quality risk management, and overall pharmaceutical quality systems. They have played some of the most important roles in this regard [3].

Subsequently, the International Council for Harmonisation (ICH) developed new guidelines known as Q 14-Analytical Procedure Development. The purpose of these guidelines was to standardise the scientific methodologies that were utilised in the process of Analytical Procedure Development and to outline the fundamental principles that govern the process of Analytical Procedure Development. This new guideline is intended to improve regulatory communication between industry stakeholders and regulatory authorities. Its goal is to promote approval processes that are more efficient, scientifically rigorous, and risk-based.

Additionally, it aims to improve management of post-approved adjustments to analytical techniques. The International Council for Harmonisation (ICH) Q2(R2) provides direction on how to create, submit, and retain evidence that demonstrates the appropriateness of an analytical technique for its intended application, particularly in the context of product quality assurance.Guidelines for the development and validation of analytical techniques that are used in evaluating the quality of drug substances and drug products throughout their lifetime are specified in ICH Q14 and ICH Q2(R2), respectively. These guidelines provide a detailed description of the relevant procedures

[4].

The Quality by Design (QbD) methodology is a methodical approach to development that begins with predetermined goals and places a strong focus on both product and process knowledge, in addition to process control. The foundation of this strategy is firmly established on reasonable scientific principles and high-quality risk management. It is the goal of this idea to ensure that medicines are of a high quality by employing cutting-edge approaches in the process of designing, developing, and producing drugs and other medicinal goods. Currently, the industry, regulatory organisations, and academic institutions are investigating the possibility of applying the concepts of Quality by Design (QbD) to analytical methodologies. This application is known as Analytical Quality by Design (AQbD) [5].

The conventional method development approach typically involves a trial-and-error process for parameter determination, with robustness being evaluated one factor at a time. Analytical Qbd, on the other hand, represents a scientific approach that consistently delivers high-quality output. Table 1 delineates the features of the traditional approach and AQbd approach in analytical method development.

Table 1: Characteristics of Traditional and AQbD approach

Traditional Analytical Method development	**AQbd Method Development**
An Empirical approach for method development	The science-based approach in method implementation
The validation process ensures the robustness of the method	The assessment of method robustness is conducted during the developmental phase.
Inadequate comprehension of critical parameters	Focus on critical parameters utilizing a riskbased approach
Variability in results of Output variables	Consistent results of output variables within design space
Increase in cost of the method due to revalidation during method transfer	A cost-effective approach that circumvents the necessity for revalidation.

Statistical tools are not utilized in the development of the method	Utilization of statistical tools is imperative for the development of robust methodologies.
Limited comprehension of the method development process.	Enhanced understanding of the method development process.
Optimization is constrained by specific settings.	Optimization involves exploring a wider range of conditions to identify the best and most reliable method settings.

2. Stages of Analytical QbD

The adoption of Quality by Design (QbD) presents an opportunity for attaining regulatory flexibility, contingent upon the attainment of robustness, product quality, and a comprehensive understanding of analytical methods. The practice of Analytical QbD encompasses the indispensable elements as presented in Figure 1[6, 7].

Figure 1: Stages of Analytical QbD

2.1 Background Knowledge and Introduction of Study Plan

A full awareness of product and process subtleties, analytical methodologies, control strategies, and a smooth bridge approach for transferring between analytical methods are all included in the fundamental information that is included in the study plan. Having this prior information reduces the likelihood of adverse outcomes and gives the procedure a higher level of quality.

During the process of creating techniques for analysing related chemicals, it was essential to conduct a complete literature research in order to gather information on the physical and chemical properties, polarity, solubility, degradation processes, and current analytical methods of the compounds.

In addition, it was of the utmost importance to have a thorough understanding of the regulatory framework, notably the ICH rules.

Take, for instance: New method: Analytical Qbd for the identification of associated substances and degradation products of cabotegravir using ultra-high-performance liquid chromatography [9]. The physicochemical features, solubility, degradation routes of cabotegravir, and available analytical procedures were learnt about in the knowledge space that was obtained.

2.2 Analytical Target Profile (ATP)

The Analytical Target Profile (ATP) is a crucial tool for developing analytical methods, defining the standard for measurable values and focusing on the target measurement uncertainty (TMU). The ATP is based on the need to establish guidance for developing and validating techniques and ensuring flexibility in testing methodologies. Performance characteristics include all validation parameters of ICH guidelines, with accuracy and precision being the predominant and essential performance characteristics [10]. The Analytical Target Profile (ATP) serves as the driving force behind selecting analytical techniques, allowing for continuous monitoring and improvement of the analytical process throughout the lifecycle [11]. For example, for developing an in vitro release test method for semi-solid topical formulations, the Analytical Target Profile (ATP) includes performance criteria such as accuracy, method precision, linearity, range, cumulative amount released at the end of the test, and robustness. The target profile includes accuracy levels of 90-110%, method precision of RSD less than 10%, linearity of R suare>0.97, range over the specified range, robustness less than 15%, and cumulative drug release over 70% [12].

2.3 Selection of Analytical technology and its objective

The objectives and purpose of a method must be clearly defined from the beginning to align with the QbD principle. Analytical techniques must be chosen considering the sample analysis environment and performance criteria outlined in ICH guidelines for ATP [13]. Alternative analytic technologies may also meet ATP requirements, allowing flexibility in method selection and transfer. For instance, HPLC is the most common method for determining drug substance in oral dosage form, and the performance characteristics of ATP can be applied to other methodologies [14].

2.4 Identification of Critical Quality attributes from analytical Target profile

Critical Quality Attributes (CQA) are a pharmaceutical product's essential chemical, physical, biological, or microbiological characteristics that must meet precise standards to ensure high quality [15]. Critical Method Parameter (CMP) refers to a process parameter characterized by its variability, which directly impacts a Critical Quality Attribute (CQA). Monitoring and controlling the CMP is essential to ensure that the process consistently yields the desired quality output [16]. Each Analytical Technique has a different CMP (Table 2) [17].

Table 2: CMP and CQA for Analytical Methods

Analytical method	Critical method parameters	Critical Quality Attributes
HPLC and UPLC	Column(dimensions, particle size, manufacture), flow rate, Column oven temperature, Buffer, Buffer concentration, pH of mobile phase, Organic modifier, detection wavelength	Retention time, Tailing factor, Peak area, Resolution, Plate count, Percentage recovery
Gas Chromatography	Column(dimensions and particle size, manufacture), , flow rate, carrier gas, split flow, Oven temperature program, Injector temperature, type of injector liner	Retention time, Tailing factor, Peak area, Resolution, Plate count, Percentage recovery
TLC and HPTLC	Plate stationary phase, coating,thickness, development distance, the temperature of solvent mixture, the composition of mobile phase, sample solution volume, size and shape of spot, drying time, visualization technique, saturation time, activation time	Retardation factor, peak area, peak height, Resolution, Percentage recovery
UV Spectroscopy	Wavelength, solvent, scanning speed, sampling interval, slit width	Absorbance

2.5 Risk Management Process

Quality risk management is a systematic process that enhances science-based decision-making regarding risks, following ICH Q9 guidelines. This framework establishes a rigorous analytical procedure to mitigate suboptimal performance risks and ensure accurate reporting of results. Risk assessment involves identifying, analyzing, and evaluating potential risks using analytical methodology, literature reviews, analytical experience, and established scientific principles [18]. The outcome can be presented numerically or qualitatively through descriptors. Risk assessment is conducted at the early stages of analytical method development, and the next step is risk communication with decision-makers and documentation to support continuous improvement of analytical procedure performance. Various management tools, such as flow charts, Ishikawa diagrams, FMEA, FMECA, Fault Tree Analysis, HACCP, HAZOP, PHA, risk ranking and filtering, and statistical tools, are used in accordance with ICH Q9 guidelines [19].

2.6 Design of Experiments (DoE)

Experimental design is a systematic method used to optimize operational parameters and improve chromatographic separation efficacy. It focuses on identifying and optimizing critical variables to achieve resilient outcomes and reduce the number of experimental iterations. The main objectives of experimental design in analytical processes are to achieve optimal and valid outcomes with minimal effort, duration, and resources [20]. Experimental design has two types: screening design and optimization design. Screening designs identify primary factors significantly impacting Critical Quality Attributes, such as fractional factorial design, PlackettBurman, and Taguchi designs [21]. Optimization designs further optimize these factors. Response surface methodology (RSM) is a collection of statistical and mathematical techniques used for developing, improving, and optimizing processes. RSM is particularly useful in understanding the relationship between multiple variables and the response of the analytical method. Common response surface designs include Full Factorial, Central composite, and Box Behnken designs. These designs offer a systematic approach to studying the impact of up to 9 factors on a given process or outcome [22].

2.7 Creating and interpreting the Method Operable Design Region (MODR)

After adjusting the analytical parameters, the next important step is to optimize the parameter range using computer software and virtual screening. This process aims to define the method operable design region (MODR) or design space [23]. The MODR represents the region that meets the preset acceptance criteria within the allowable variation range of Critical Method Parameters (CMP) and is established in a multi-dimensional space based on the relationship between CMP and Critical Quality Attributes (CQAs) [24]. Ultimately, the MODR ensures the appropriate performance of the analytical procedure. The MODR is a risk-based, multivariate methodology to evaluate the influence of various factors on procedure performance and to prevent the risk of critical procedure parameter deviation to achieve the desired results [25]. Any approach that works within the defined parameter values and MODR limits has the potential to yield high-quality results [26].

2.8 Analytical Method Control Strategy

As per the definition in ICH Q10, a control strategy denotes a meticulously planned array of controls derived from the contemporary comprehension of both product and process, which guarantees the efficacy of the process and the quality of the product. The controls may encompass parameters and attributes associated with drug substance and drug product materials and components, facility and equipment operating conditions, in-process controls, finished product specifications, and the methods and frequency of monitoring and control. The formulation of analytical procedure controls is based on empirical data from "CAA," "DoE," and "MODR" to establish a closer link between the procedural objective and its performance [27]. The strategy for controlling the analytical procedure involves overseeing the analytical parameters and carrying out a system suitability test (SST) as part of the analytical procedure description. The description of the analytical procedure should outline the necessary steps for conducting each analytical test, including sample preparation, use of reference materials and reagents, apparatus, formula generation, calibration curve creation for result calculation, and other essential steps [28].

2.9 Method Validation

Once the control strategy for the method has been finalized, it is crucial to test and verify the method's performance through formal validation. The objective of analytical method validation is to demonstrate its suitability for the intended purpose. The extent of validation and the acceptance criteria depend on the development phase, the method's purpose, and the type of method used. Typical validation characteristics are based on the requirements outlined in ICH Q2(R2) [29].

2.10 Continual Method Monitoring

To ensure the reliability of analytical methods, it is essential to continuously monitor their performance. This involves establishing standards for sample analysis, tracking system suitability, and analyzing reference standard lot data [30]. Visualizing and tracking product data can provide valuable insights into method performance. Statistical process control charts can visually demonstrate the stability and capability of a process. It is crucial to monitor method performance and make any necessary adjustments to enhance the analytical procedure.

Improving method performance to take advantage of new technology, such as advancements in instrumentation leading to increased throughput, may be beneficial. Conversely, method performance may decline over time due to gradual changes in chromatographic column chemistry or performance. Employing a science- and risk-based approach can help in developing a well-understood method control strategy, contributing to the continuous improvement of methods in routine operation. This approach can help reduce industry and regulatory burden while ensuring sustained method performance [31].

3. Conclusion

As a conclusion, the use of an Analytical Quality by Design (AQbD) methodology for the creation of techniques provides a multitude of benefits in comparison to the utilisation of conventional empirical methods. A more comprehensive grasp of important parameters is ensured by the focus placed on a science-based approach, which ultimately results in a more robust method implementation. Through the process of evaluating the robustness of the approach throughout the development phase, AQbD makes it easier to produce consistent outcomes in output variables within the design space that has been previously specified. The use of this technique not only guarantees the quality and dependability of analytical methods, but it also reduces the amount of revalidation that is required, which makes it a methodology that is both cost-effective and efficient.The adoption of international norms, such as ICH Q14 and ICH Q2(R2), is an essential component in the process of improving regulatory communication between regulatory authorities and industry stakeholders. The purpose of these recommendations is to simplify and standardise the scientific approaches that are utilised in the process of Analytical Procedure Development, which will ultimately make it possible to have approval procedures that are more robust and risk-based. These recommendations also add to the overall quality and reliability of drug assessment processes by enhancing the management of postapproval modifications to analytical techniques. This is accomplished via the improvement of the management of these changes.In general, the methodical approach of AQbD is in accordance with the more general concepts of Quality by Design (QbD), and it highlights the industry's dedication to expanding pharmaceutical research and quality management. Pharmaceutical developers are able to obtain a more thorough understanding of crucial parameters through the application of AQbD, which ultimately results in more robust analytical procedures and ensures the quality and dependability of medicinal substances and products throughout their entire lifespan.

4. Conflict of Interest

None

5. References

1. Center for Drug Evaluation and Research, (2015) U. S. Food and Drug Administration. Analytical Procedures and Methods Validation for Drugs and Biologics. Rockville, MD: FDA
2. Center for Drug Evaluation and Research, (2015) U. S. Food and Drug Administration. Pharmaceutical Quality for the 21st century: a Risk-Based Approach Progress Report. Rockville, MD: FDA.
3. Yu, L. X., Amidon, G., Khan, M. A., Hoag, S. W., Polli, J., Raju, G. K., & Woodcock, J. (2014). Understanding pharmaceutical quality by design. *The AAPS journal*, *16*(4), 771– 783. https://doi.org/10.1208/s12248-014-9598-3
4. International Conference of Harmonization (2023). Q2R2/Q14 step 4 Presentation
5. British Pharmacopeia, AQbd Guidance. https://www.pharmacopoeia.com/guidance/aqbd
6. International Conference of Harmonization ICH (2009) Q8 (R2). Pharmaceutical Development, Current Step4 version.

7. International Conference of Harmonization ICH (2023) Q14. Analytical Procedure Development, Final version.
8. Vogt, F G., Kord, AS (2011).Development of Quality-By-Design Analytical Methods. Journal of Pharmaceutical Sciences, 100(3), 797-812.https://doi.org/10.1002/jps.22325
9. Kovac, L., Casar, Z., Lusin TT., RoskarR.(2022). Development of an Analytical Method for Determination of Related Substances and Degradation Products of Cabotegravir Using Analytical Quality by Design Principles, 10, 8896-8905.https://doi.org/10.1021/acsomega.1c07260
10. Ramalingam, P., Jahanavi, B.,(2019) Chapter 5: QbD Considerations for Analytical Development, Beg, S., Hasnain, M S., (eds), Pharmaceutical Quality By Design, Academic Press. 77-108
11. Shaik,A A., Nagaraju, P (2023) Analytical QBD Approach to Redefine the Quality of Pharmaceuticals: A Review. J. Pharm. Res.;22(4):178–185. https://doi.org/10.18579/jopcr/v22.4.81
12. Ramalingam, P, Kalva, B., Yiragamreddy, PR(2015) Analytical Quality by Design: A Tool for Regulatory Flexibility and Robust Analytics, *International Journal of Analytical Chemistry*, 1- 9. https://doi.org/10.1155/2015/868727
13. Ermer,J(2018) ,Analytical Target Profile: establishment of precision requirements for assay,Journal of Pharmaceutical and Biomedical Analysis,160, 73-79. https://doi.org/10.1016/j.jpba.2018.07.035.
14. Szoleczky R, Kovács A, Berkó S, Budai-Szűcs M. An Analytical Target Profile for the Development of an In Vitro Release Test Method and Apparatus Selection in the Case of Semisolid Topical Formulations. *Pharmaceutics*. 2024; 16(3):313. https://doi.org/10.3390/pharmaceutics16030313
15. Jackson, Patrick & Borman, Phil & Campa, Cristiana & Chatfield, Marion & Godfrey, Mark & Hamilton, Peter & Hoyer, Walter & Norelli, Francesco & Orr, Rachel & Schofield, Timothy. (2019). Using the Analytical Target Profile to Drive the Analytical Method Lifecycle. Analytical Chemistry. 91. 10.1021/acs.analchem.8b04596.
16. Susmitha, A., Rajitha, G., & Eri, G. K. (2023). A comprehensive review on QbD driven analytical procedures developed for the analysis of various drugs. *Journal of Liquid Chromatography & Related Technologies*, *46*(1–5), 12–36. https://doi.org/10.1080/10826076.2023.2204238
17. Nitin Kumar, Sangeetha d (2020), Analytical method development by using QbD- An emerging approach for robust analytical method development, Journal of Pharmaceutical Sciences and Research, 12(10),1298-1305.
18. International Conference of Harmonization ICH (2023) Q9(R1). Quality Risk Management

19. Sahu, P. K., Ramisetti, N. R., Cecchi, T., Swain, S., Patro, C. S., & Panda, J. (2018). An overview of experimental designs in HPLC method development and validation. *Journal of pharmaceutical and biomedical analysis*, *147*, 590–611. https://doi.org/10.1016/j.jpba.2017.05.006
20. Patel, K.Y., Dedania, Z.R., Dedania, R.R. *et al.* QbD approach to HPLC method development and validation of ceftriaxone sodium. *Futur J Pharm Sci* **7**, 141 (2021). https://doi.org/10.1186/s43094-021-00286-4
21. Athar Shamim, Mohammad Javed Ansari, Alhussain Aodah, Muzaffar Iqbal, Mohd. Aqil, Mohd. Aamir Mirza, Zeenat Iqbal, and Asgar Ali*ACS Omega* **2023** *8* (24), 2161821627DOI: 10.1021/acsomega.3c00956
22. Sha'at, M., Spac, A. F., Stoleriu, I., Bujor, A., Cretan, M. S., Hartan, M., &Ochiuz, L. (2022). Implementation of QbD Approach to the Analytical Method Development and Validation for the Estimation of Metformin Hydrochloride in Tablet Dosage Forms by HPLC. *Pharmaceutics*, *14*(6), 1187. https://doi.org/10.3390/pharmaceutics14061187
23. Sandhu, P. S., Beg, S., Katare, O. P., & Singh, B. (2016). QbD-Driven Development and Validation of a HPLC Method for Estimation of Tamoxifen Citrate with Improved Performance. *Journal of chromatographic science*, *54*(8), 1373–1384. https://doi.org/10.1093/chromsci/bmw090
24. Beg, S., Chaudhary, V., Sharma, G., Garg, B., Panda, S. S., & Singh, B. (2016). QbDoriented development and validation of a bioanalytical method for nevirapine with enhanced liquid-liquid extraction and chromatographic separation. *Biomedical chromatography : BMC*, *30*(6), 818–828. https://doi.org/10.1002/bmc.3613
25. Kaur, R., Saini, S., Patel, A., Sharma, T., Kaur, R., Katare, O. P., & Singh, B. (2021). Developing a Validated HPLC Method for Quantification of Ceftazidime Employing Analytical Quality by Design and Monte Carlo Simulations. *Journal of AOAC International*, *104*(3), 620–632. https://doi.org/10.1093/jaoacint/qsab014
26. Stojanović, Jevrem &Krmar, Jovana & Protić, Ana &Svrkota, Bojana &Djajić, Nevena &Otašević, Biljana. (2021). Experimental design in HPLC separation of pharmaceuticals. Arhiv za farmaciju. 71. 279-301. 10.5937/arhfarm71-32480.
27. Douglas C Montgomery (2023), Design and Analysis of Experiments, 8th edition, chapter 11-Response Surface Methodology, pp.498
28. Park, G., Kim, M. K., Go, S. H., Choi, M., & Jang, Y. P. (2022). Analytical Quality by Design (AQbD) Approach to the Development of Analytical Procedures for Medicinal Plants. *Plants (Basel, Switzerland)*, *11*(21), 2960. https://doi.org/10.3390/plants11212960.
29. International Conference of Harmonization ICH (2008) Q10 PharmaceuticalQuality System, Current Step4 version.
30. De sousa, J., Holt, D. A., & Butterworth, P. A. (2018). Chapter 10 Analytical Method Design, Development, and Lifecycle Management. *Pharmaceutical Quality by DEsugn: A Practical Approach*,

257-279. https://doi.org/10.1002/9781118895238.ch10Editor(s): Walkiria S. Schlindwein, Mark Gibson

31. International Conference of Harmonization ICH (2023) Q2 (R2). Validation of analytical procedures, Final version.